

Remarks

Applicants request consideration of the above-referenced patent application.

I. Amendments to Claims

Claims 8-11, 13, and 15 are pending. This amendment amends all these claims. The claims, including the amendments, are shown in the previous section. Applicants submit that the amendments do not introduce new matter. Specifically:

In claim 8, the preamble has been amended to recite the isomers, enantiomers, tautomers, racemates, polymorphs, and salts encompassed by claim 8. This amendment is intended to make claim 8 easier to read, and is supported by claim 8 itself (as originally filed), as well as Applicants' specification at, for example, page 26, line 21 to page 27, line 16.

In claim 8, the A-B ring structure has been incorporated into Formula I. This amendment is intended to make claim 8 easier to read. It also addresses the concern raised in Paragraph 3(b) of the Office action regarding the redundant Z¹.

In claim 8, the "A" and "B" in the A-B ring structure are unnecessary, and therefore have been removed.

In claim 8, the R^b definition has been incorporated into Formula I. This amendment is intended to make claim 8 easier to read.

The wording of the Z₁/Z₂ definitions has been amended to be more consistent with the Z₁/Z₂ definitions in Applicants' specification at, for example, page 8, lines 1-13.

In claim 8, "n" is used three different times, *i.e.*, for Formula I, R^c, and X. These definitions are identical. To remove the redundancy, two of the definitions have been removed, and the remaining definition has been amended to indicate that each "n" is defined independently of the other.

In claim 8, "thioalkyl" has been replaced with "alkylthio" in the Z₁/Z₂ and R^c definitions. This amendment corrects an obvious error, and is supported by Applicants' specification at, for example, page 17, lines 26-27; and page 24, lines 16-17.

In claim 8, many of the A¹ structures have been amended to incorporate the various sub-definitions into the structures. This amendment is intended to make claim 8 easier to read.

In claim 8, many of the structures have been amended to show, in a more consistent manner, the bonds that connect the structures to the remaining portion of the compound.

Claim 10 has been amended to expressly include compositions comprising isomers, enantiomers, tautomers, racemates, polymorphs, and salts recited in claim 8.

Claim 10 also has been amended to characterize the amount of the compound, enantiomer, tautomer, racemate, polymorph, or salt of claim 8 in terms of inhibiting or antagonizing $\alpha_v\beta_3$ or $\alpha_v\beta_5$. This amendment is supported by Applicants' specification at, for example, page 5, lines 1-6; page 9, lines 1-6; and page 15, lines 4-16.

Claims 11, 13, and 15 have been amended to expressly include methods of treatment using isomers, enantiomers, tautomers, racemates, polymorphs, and salts recited in claim 8.

Other amendments rephrase the claims, remove redundancies or unnecessary terms, or correct grammatical or obvious errors. Applicants submit that such amendments are permissible under MPEP §2163.07.

Applicants reserve the right to pursue any canceled subject matter (or any other subject matter disclosed in this application) in one or more later-filed divisional and/or continuation applications.

II. Response to rejection of claims 10, 11, 13, and 15 under 35 U.S.C. §112 (first paragraph) in Section 1 of the Office action

Claims 10, 11, 13, and 15 have been rejected under 35 U.S.C. §112 (first paragraph) for failure to enable their entire scope. Applicants request withdrawal of this rejection.

Claim 10, as amended, is directed to a pharmaceutical composition comprising a compound, enantiomer, tautomer, racemate, polymorph, or salt of claim 8 in an amount that inhibits or antagonizes $\alpha_v\beta_3$ or $\alpha_v\beta_5$. Applicants submit that this claim is enabled. To be enabled under 35 U.S.C. § 112 (first paragraph), the specification must teach those skilled in the art how to make and use the claimed invention without "undue experimentation". See MPEP §2164.01. In the instant application, Applicants have provided assays for analyzing the inhibitory effectiveness of a compound-in-question, as well as data demonstrating the use of those assays with compounds that Applicants have prepared in accordance with this invention. See, e.g., Applicants' specification, page 104, line 1 to page 110, line 4. In addition, Applicants have provided a detailed discussion relating to preparation and use of the claimed pharmaceutical compositions. See, e.g., Applicants' specification, page 27, line 17 to page 33, line 45. This

discussion, for example, includes details relating to examples of contemplated dosages and dosage regimens for such compositions, examples of contemplated routes of administration for such compositions, examples of various contemplated adjuvants that may be included in such compositions, and examples of additional contemplated active ingredients that may be included in such compositions. One skilled in the art would have been able to use this discussion to prepare the compositions recited in claim 10. Although such preparation may, in some instances, require experimentation, such experimentation is the type that one skilled in the art would typically engage in when preparing pharmaceutical compositions. Thus, Applicants submit that it is not the type that should be construed as "undue experimentation":

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.

See MPEP §2164.01. In the absence of such experimentation being "undue", claim 10 must be found to be enabled.

Claims 11, 13, and 15 are directed to methods of using a compound, enantiomer, tautomer, racemate, polymorph, or salt of claim 8 to treat the various conditions recited in those claims. The rejection of these claims is premised on reported findings in Reynolds, L.E., et al., "Enhanced pathological angiogenesis in mice lacking $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrins", *Nature Medicine*, 8(1), 27-34 (2002). These findings relate to purported tumorigenesis and tumor growth in the absence of $\alpha_v\beta_3$ and $\alpha_v\beta_5$. From this, the Office action concludes that the claimed methods, which use inhibitors and antagonists of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ to treat cancer-related conditions, is not enabled. Applicants submit that this reliance on Reynolds, et al. is improper. First, even in the context of their own reported findings, Reynolds, et al. expressly state that they do not dispute the efficacy of $\alpha_v\beta_3$ antagonists in angiogenesis inhibition:

The efficacy of $\alpha_v\beta_3$ antagonists in angiogenesis inhibition is not in dispute here
--- such inhibitors may yet prove to be effective therapeutics.

See Reynolds, et al., page 33. In addition, references published subsequent to Reynolds, et al. have called into question the dependability of Reynolds, et al.'s reported findings and conclusions. For example, Sheppard hypothesizes that Reynolds, et al.'s reported enhanced tumor angiogenesis results may have been influenced compensatory up-regulation of the

vascular endothelial growth factor receptor II in the mice. See Sheppard, D., "Endothelial integrins and angiogenesis: not so simple anymore", *J. Clin. Invest.*, 110(7): 913-914 (2002) (enclosed). And Weng, et al. hypothesize that Reynolds, et al.'s reported results may have been influenced by increased expression of the vascular endothelial growth factor receptor Flk-1, which is proatherogenic in apoE-null mice. See Weng, S., et al., " β 3 integrin deficiency promotes atherosclerosis and pulmonary inflammation in high-fat-fed, hyperlipidemic mice", *Proc. Natl. Acad. Sci. USA*, 100(11), 6730-6735 (2003) (enclosed).

Applicants' specification provides a detailed background discussion relating to the role of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ with respect to conditions listed in claims 11, 13, and 15. See Applicants' specification at, for example, pages 1-4. Applicants' specification also provides a detailed instructions for using their invention to treat these conditions. This includes discussion relating to assessing the effectiveness of compounds to inhibit and antagonize $\alpha_v\beta_3$ and $\alpha_v\beta_5$. See, e.g., Applicants' specification, page 104, line 1 to page 110, line 4. It also includes discussion relating to pharmaceutical compositions and their use in the claimed methods. See, e.g., Applicants' specification, page 27, line 17 to page 33, line 45. For example, Applicants' specification provides details relating to examples of contemplated dosages and dosage regimens for such compositions, examples of contemplated routes of administration for such compositions, examples of various contemplated adjuvants that may be included in such compositions, and examples of additional contemplated active ingredients that may be included in such compositions. One skilled in the art would have been able to use this discussion to practice the claimed methods of claims 11, 13, and 15. Although practicing such methods may, in some instances, require some experimentation, such experimentation is the type that one skilled in the art would typically engage in when preparing a pharmaceutical composition. As noted above, such experimentation is not the type that should be construed as "undue experimentation". Thus, claims 11, 13, and 15 must be found to be enabled.

III. Response to rejection of claims 10, 11, 13, and 15 under 35 U.S.C. §112 (second paragraph) in Section 2(g) of the Office action

Claims 10, 11, 13 and 15 have been rejected under 35 U.S.C. §112 (second paragraph) for being indefinite in view of the same reasons set forth in the office action relating to

enablement. Applicants request withdrawal of this rejection. Under 35 U.S.C. §112 (second paragraph), a claim must only set out and circumscribe its subject matter with a reasonable degree of clarity and particularity. See MPEP 2173.02. Breadth of a claim does not equate to indefiniteness. See MPEP 2173.04.

At the outset, Applicants believe that the enablement rejection of claims 10, 11, 13, and 15 should be withdrawn, and have provided their reasoning in the above section supporting this belief. Given that the indefiniteness rejection is premised on the merits of the enablement rejection, Applicants submit that the indefiniteness rejection should be withdrawn for at least the same reasons that the enablement rejection should be withdrawn.

Moreover, it should be noted that there is no indication in this rejection (or the enablement rejection upon which this rejection is based) as to which terms in claims 10, 11, 13, or 15 are indefinite. Applicants submit that all such terms satisfy 35 U.S.C. §112 (second paragraph), particularly when read in view of Applicants' detailed description.

IV. Response to rejection of claim 15 under 35 U.S.C. §112 (second paragraph) in Section 2(h) of the Office action

Claim 15 has been rejected under 35 U.S.C. §112 (second paragraph) as being indefinite for being directed to a combination therapy that includes administering a "chemotherapeutic agent". Applicants request withdrawal of this rejection. Under 35 U.S.C. §112 (second paragraph), claim 15 must only set out and circumscribe its subject matter with a reasonable degree of clarity and particularity. In determining whether claim 15 meets this threshold, Applicants' disclosure must be taken into account:

Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A)
The content of the particular application disclosure; . . .

See MPEP 2173.02. Here, Applicants have provided over three pages of detailed description relating to contemplated chemotherapeutic agents. See, e.g., Applicants' specification at page 30, line 15 to page 33, line 45. This text includes various details relating to common classes of chemotherapeutic agents. It also provides a plethora of specific examples of contemplated chemotherapeutic agents, as well as median dosages for each of those agents. See, e.g.,

Applicants' specification at page 31, line 30 to page 33, line 45. One skilled in the art, especially when armed with these teachings, would understand the scope of "chemotherapeutic agent". This is particularly true here, given that claim 15 recites the specific condition being treated (*i.e.*, neoplasia). This, after all, provides context in which the term "chemotherapeutic agent" is being used.

V. Response to rejection of claims 8, 10, 11, 13, and 15 under 35 U.S.C. §112 (second paragraph) in Section 3(g) of the Office action

Claims 8, 10, 11, 13, and 15 have been rejected under 35 U.S.C. §112 (second paragraph) for reciting an A-B structure having a redundant Z₁ moiety. Applicants request withdrawal of this rejection.

Applicants have amended claim 8 to incorporate the A-B ring structure into Formula I. This amendment removes the redundant Z₁ moiety, thus mooted this rejection.

Claims 10, 11, 13, and 15 depend from claim 8. This rejection therefore is mooted as to those claims for at least the same reasons as claim 8.

VI. Response to double-patenting rejection of claims 8-11, 13, and 15

Claims 8-11, 13, and 15 have been provisionally rejected under the judicially-created doctrine of obviousness-type double patenting over the claims of U.S. Application No. 10/363,070. Because the claims of U.S. Application No. 10/363,070 and the instant application have not yet been found to be otherwise allowable, Applicants submit that this rejection must remain provisional. And a requirement for any further response from Applicants at this point would be premature. See MPEP 804. Applicants will address this issue (to the extent necessary) once the claims have been found to be otherwise allowable.

VII. Response to rejection of claims 8, 10, 11, 13, and 15 under 35 U.S.C. §112 (first paragraph) in Section 5 of the Office action

Claims 8, 10, 11, 13, and 15 have been rejected under 35 U.S.C. §112 (first paragraph) for failure of the A1 definition (as amended by Applicants' Amendment B) to comply with the written description requirement. Applicants request withdrawal of these rejections.

At the outset, Applicants have amended the A¹ structures to incorporate the sub-definitions into the structures to make claim 8 easier to read. Some of these structures also have been amended to be more consistent with the structures and sub-definitions in claim 8, as originally filed. Applicants submit that these amendments obviate the concerns raised in Sections 5(a), 5(b), 5(c), 5(d), 5(g), 5(h), and 5(i) of the Office action. Specifically:

- i) The amended structures corresponding to the structure-at-issue in Section 5(a) of the Office action have either an NH or an NCH₃ at the "B¹" position when B¹ is NR^a. This is more consistent with, for example, the A¹ definition in claim 8 (as originally filed), which defines "B" for that structure as including NR, and "R" as H or CH₃. The amended structures also have either an OH or OCH₃ at the "R⁷⁹" position when R⁷⁹ is OR^a. This is more consistent with, for example, the A¹ definition in claim 8 (as originally filed), which defines "R" as including OR; and "R" as H or CH₃.
- ii) The amended structures corresponding to the structure-at-issue in Section 5(b) of the Office action have either an H or a CH₃ at the "R⁷⁹" position. This is more consistent with, for example, the A¹ definition in claim 8 (as originally filed), which defines "R" as H or CH₃.
- iii) The amended structures corresponding to the structure-at-issue in Section 5(c) of the Office action have either an NH, O, or S at the "B²" position. This is more consistent with, for example, Applicants' specification at, for example, pages 12 (line 3) and 14 (line 2), which defines "B" as NH, O, or S. Although claim 8 (as originally filed) and Applicants' specification at page 15 (line 2) define "B" as N or CH, this is an obvious typographical error, as evidenced by the corresponding definitions on pages 12 (line 3) and 14 (line 2), and the fact that the "B" position is a divalent position (NH, O, and S are all divalent, whereas N and CH are trivalent).

- iv) The amended structures corresponding to the structure-at-issue in Section 5(d) of the Office action have either an H or a CH₃ at the "R⁷⁹" position. This is more consistent with, for example, the A¹ definition in claim 8 (as originally filed), which defines "R" as H or CH₃.
- v) The amended structures corresponding to the structure-at-issue in Section 5(g) of the Office action do not include structures wherein the moiety at the "X⁷" position is CF₂. This is more consistent with, for example, the "X" sub-definition for that structure in claim 8, as originally filed. The amended structures also have either an NH or an NCH₃ at the "X⁷" position when X⁷ is NR^a. This is more consistent with, for example, the A¹ definition in claim 8 (as originally filed), which defines "X" for that structure as including NR, and "R" as H or CH₃. Finally, the amended structures have either an OCH₃, OH, or CH₃ at the "R⁷⁹" position. This is more consistent with, for example, the A¹ definition in claim 8 (as originally filed), which defines "R¹" as OCH₃, OH, or CH₃.
- vi) The amended structures corresponding to the structure-at-issue in Section 5(h) of the Office action do not include structures wherein the moiety at the "X⁸" position is CH₂ or CONR^a. This is more consistent with, for example, the "X" sub-definition for that structure in claim 8, as originally filed. The amended structures also have either an NH or an NCH₃ at the "X⁸" position when X⁸ is NR^a. This is more consistent with, for example, the A¹ definition in claim 8 (as originally filed), which defines "X" for that structure as including NR, and "R" as H or CH₃. Finally, the amended structures also have either an OCH₃, OH, or CH₃ at the "R⁷⁹" position. This is more consistent with, for example, the A¹ definition in claim 8 (as originally filed), which defines "R¹" as OCH₃, OH, or CH₃.
- vii) The amended structures corresponding to the structure-at-issue in Section 5(i) of the Office action have either an NH or an NCH₃ at the "B⁷" position when B⁷ is NR^a. This is more consistent with, for example, the A¹ definition in claim 8 (as

originally filed), which defines "B" for that structure as including NR, and "R" as H or CH₃. The amended structures also have either an OCH₃, OH, or CH₃ at the "R⁸¹" position. This is more consistent with, for example, the A¹ definition in claim 8 (as originally filed), which defines "R¹" as OCH₃, OH, or CH₃.

As to Sections 5(e) and 5(f) of the Office action, Applicants submit that the structures-at-issue are supported by Applicants' specification at, for example, page 15, line 2 (see last two structures in that line); and claim 8 (as originally filed), at page 120, line 2 (see last two structures in that line).

VIII. Response to rejection of claims 8, 10, 11, 13, and 15 under 35 U.S.C. §112 (second paragraph) in Section 6 of the Office action

Claims 8, 10, 11, 13, and 15 have been rejected under 35 U.S.C. §112 (second paragraph) as being indefinite. Applicants request withdrawal of these rejections. All these rejections stem from issues in the text of claim 8. Applicants submit that these issues have been addressed in claim 8 (and therefore also in claims 10, 11, 13, and 15). Specifically:

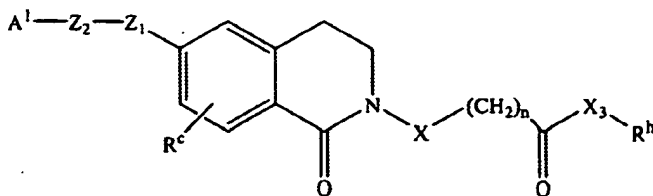
- a) The "A1" has been replaced with "A¹" in claim 8, thus obviating the rejection in Section 6(a) of the Office action. This amendment simply corrects an obvious typographical error.
- b) The first structure in claim 8 on page 5 of Applicants' Amendment B has been replaced with new structures that each more clearly identify the bond that connects the structure to the remaining portion of the compound, thus obviating the rejection in Section 6(b) of the Office action.
- c) The second structure in claim 8 in line 2 of page 4 of Applicants' Amendment B has been replaced with new structures that incorporate the "B" definition from pages 12 (line 3) and 14 (line 2) for the corresponding structure. Thus, the moiety

at the "B²" position is either NH, O, or S rather than N or CH. This amendment obviates the rejection in Section 6(c) of the Office action.

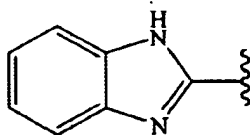
IX. Response to rejection of claims 8, 10, 11, 13, and 15 under 35 U.S.C. §102(b) in Section 7 of the Office action

Claims 8, 10, 11, 13, and 15 have been rejected under 35 U.S.C. §102(b) as being anticipated by Miller, et al. (WO 97/24117), and specifically by the compound discussed in Example 76 of Miller, et al. Applicants request withdrawal of this rejection.

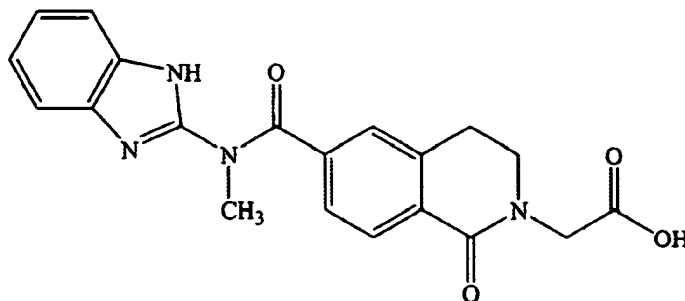
Claim 8 is directed to compounds corresponding in structure to Formula I:



A^1 is selected from various ring-comprising structures. Those ring structures, however, do not include benzoimidazolyl:

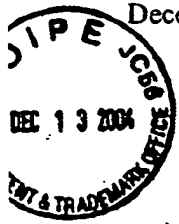


In contrast to compounds of claim 8, the compound discussed in Example 76 of Miller, et al. corresponds in structure to the following formula:



The benzoimidazolyl in this compound fails to satisfy the A^1 definition in claim 8. Thus, claim 8 is novel over the cited compound.

Claims 10, 11, 13, and 15 depend from claim 8, and are therefore novel over the cited compound for at least the same reasons as claim 8.



Applicants hereby request a 1-month extension to respond to the August 11, 2004 Office action, and have enclosed a check to cover the fee for that extension. Applicants believe that they do not owe any additional fee in connection with this filing. If, however, Applicants do owe any such fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. 08-0750. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. 08-0750.

Applicants submit that the pending claims are in condition for allowance, and request that this application be allowed. The Examiner is requested to call the Undersigned if any issues arise that can be addressed over the phone to expedite examination of this application.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 CFR § 1.8

I certify that this correspondence is being deposited with the U.S. Postal Service on **December 13, 2004** with sufficient postage as first class mail (including Express Mail per MPEP §512), and addressed to **MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450**.

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